Tetrahedron, 1958, Vol. 2, pp. 164–166. Pergamon Press Ltd., London

PRELIMINARY COMMUNICATIONS

Steroids—XC*

11α-Methyl-11β-hydroxy steroids

(*Received* 24 *September* 1957)

WE WISH to record the synthesis of several 11α-methyl-11β-hydroxy steroid hormone analogs derived by the addition of metallo-organic reagents to the C-11 position of 11-keto steroids.[1]†‡ Reaction of androstan-3β-ol-11,17-dione (I)§ (m.p. 169–171°, $[\alpha]_D$ + 125°.[1] *Anal.* Found for $C_{19}H_{28}O_3$: C, 74·56; H, 8·98) with methylmagnesium bromide in benzene-ether solution at 25° gave, in addition to the expected 17α-methylandrostane-3β,17β-diol-11-one (m.p. 218–221°, $[\alpha]_D \pm 0°$), a 30 per cent yield of a more polar by-product (II) (m.p. 164–166°, $[\alpha]_D$ − 5°. *Anal.* Found for $C_{21}H_{36}O_3$: C, 75·32; H, 10·91) to which we assign the 11α,¶17α-dimethylandrostane-3β,11β,17β-triol structure, since it exhibited no carbonyl absorption in the infrared and differed from 17α-methylandrostane-3β,-11β,17β-triol.** Substitution of methyllithium in ether for methylmagnesium bromide gave an 80 per cent yield of the same 11,17-dimethyl compound.

Pyridinium-chromate oxidation of (II) smoothly led to the 3-keto compound, 11α,17α-dimethyl-androstane-11β,17β-diol-3-one (III) (m.p. 202–205°, $[\alpha]_D$ + 6°. *Anal.* Calcd. for $C_{21}H_{34}O_3$: C, 75·40; H, 10·24. Found C, 75·03; H, 10·08).

Confirmation and extension of 11-methyl addition was provided by the reaction with methyl-lithium of mono-functional 11-keto compounds, such as pregnan-11-one[2] and allopregnan-11-one,[2] which yielded ketone-free products, resistant to chromic acid oxidation, e.g. 11α-methyl-allopregnan-11β-ol (m.p. 112–113°, $[\alpha]_D$ + 23°. *Anal.* Found for $C_{22}H_{38}O$: C, 83·17; H, 11·77; O, 4·89).

Although a number of more complex molecules failed to react at C-11 with methyllithium, 11α-methyl-11β-hydroxytestosterone (IV) was readily derived by the following reaction sequence. Adrenosterone 3,17-bis*cyclo*ethylene ketal[3] was converted to 11α-methyl-3,17-di*cyclo*ethylenedioxy-Δ^5-androsten-11β-ol (V) (m.p. 192–194°, $[\alpha]_D$ − 94° (pyr.). *Anal.* Found for $C_{24}H_{36}O_5$: C, 70·90; H, 9·01) by reaction with methyllithium in ether-tetrahydrofuran solution. Hydrolysis of the ketal moieties of (V) in 70 per cent acetic acid gave 11α-methyl-Δ^4-androsten-11β-ol-3,17-dione (VI) (m.p. 151–152°, $[\alpha]_D$ + 162°, $\lambda_{max.}^{EtOH}$243 mμ, log ε 4·19. *Anal.* Found for $C_{20}H_{28}O_3$: C, 75·61;

* Paper LXXXIX, A. Bowers, H. J. Ringold and R. I. Dorfman *J. Amer. Chem. Soc.* **79**, 4556 (1957).

† Ruzicka *et al.* reported the addition of methylmagnesium iodide to the triterpene, 11-keto-β-amyrin, but it should be noted that they were dealing with an α,β-unsaturated carbonyl function.

‡ The addition of methylmagnesium bromide to a steroidal C-11 carbonyl function was reported in the case of the ring A unsubstituted androstane-11,17-dione in a talk given at the Dallas Meeting of the American Chemical Society, April 1956, by Dr. John C. Babcock of The Upjohn Company.

§ Prepared by sodium bismuthate cleavage of allopregnane-3β,17α,21-triol-11,20-dione.

|| All melting points are uncorrected and rotations were determined at 20° in chloroform. We are grateful to Mrs. E. Necoechea, Miss G. Monroy and Miss J. Lisci for their valuable technical assistance and to Mr. E. Avila for determination of rotations and spectra.

¶ Carbanion addition would be expected to follow the stereochemical course of hydride attack and thus yield the 11α-methyl compound.

** This compound, prepared by the addition of methylmagnesium bromide to androstane-3β,11β-diol-17-one, melts at 247–251°, $[\alpha]_D$ + 12°. *Anal.* Found for $C_{20}H_{34}O_3$: C, 74·14; H, 10·52. While reduction of hindered ketones with methyl Grignard reagents has not been described nor would such reduction appear to be mechanistically feasible, in contrast to the corresponding ethyl reagent, we did not wish to discount this possibility *a priori*.

[1] L. Ruzicka, G. Müller and H. Schellenberg *Helv. Chim. Acta* **22**, 767 (1939).
[2] F. Sondheimer, E. Batres and G. Rosenkranz *J. Org. Chem.* **22**, 1090 (1957).
[3] S. Bernstein, R. Littell and J. H. Williams *J. Amer. Chem. Soc.* **75**, 1481 (1953).

H, 8·89) which was converted to the testosterone analog (IV) (m.p. 255–256°, $[\alpha]_D$ + 111°, $\lambda_{max.}^{EtOH}$ 244 mμ, log ε 4·18. *Anal.* Found for $C_{20}H_{30}O_2$: C, 75·24; H, 9·62) by selective reduction[4] with sodium borohydride in methanol at 0°. Alternately, reaction of the 3,17-dione (VI) with pyrrolidine in methanol gave the 3-enamine,[5] (11α-methyl-3-(N-pyrrolidyl)-$\Delta^{2,5}$-androstadien-11β-ol-17-one (VII) (m.p. 249–250°, $[\alpha]_D$ − 140° (pyr.), $\lambda_{max.}^{Ether}$ 281 mμ, log ε 4·35. *Anal.* Found for $C_{24}H_{35}NO_2$: C, 77·87; H, 9·43; N, 3·85) which, after lithium aluminum hydride reduction followed by hydrolysis, gave authentic (IV).

We shall report at a later date on further interconversions in this interesting series, as well as on the dehydration products of 11α-methyl-11β-hydroxy steroids.

Research Laboratories
Syntex, S.A.
Apartado Postal 2679
Mexico, D.F.

H. J. Ringold
E. Batres
J. A. Zderic

[4] J. K. Norymberski and G. F. Woods *J. Chem. Soc.* 3426 (1955).
[5] J. Johnson, M. Herr, J. Babcock, A. Fonken, J. Stafford and F. Heyl *J. Amer. Chem. Soc.* **78**, 430 (1956).

Steroids—XCI *

Microbiological oxidations of 19-norprogesterone

(*Received* 24 *September* 1957)

The clinical importance of 19-nor steroids such as 19-nor-17α-methyltestosterone,[1] 19-nor-17α-ethinyltestosterone (Norlutin)[1] and of the latter's $\Delta^{5(10)}$-isomer[2] is now well recognized† and these substances are all prepared on an industrial scale by modified Birch reductions[3] of aromatic precursors. The synthesis of the more complicated 19-nor analogs of 11-oxygenated adrenal hormones,[4] on the other hand, has been carried out only by adrenal incubation[4] of 19-norpregnenes or by starting with 11-oxygenated aromatic precursors[5] amenable to Birch reduction.[3] The much more attractive and direct route of attempting 11-oxygenation in the 19-nor series by microbiological means has so far only been accomplished with 19-nortestosterone[6] and is thus of no direct utility for the facile synthesis of 19-nor cortical hormones.[4] We should now like to report that 19-norprogesterone (I)[7] reacts readily with a variety of micro-organisms and that the way is now open to the synthesis of a large number of 11-oxygenated-19-nor as well as 11-oxygenated aromatic analogs of steroidal hormones of the pregnane series.

Incubation of (I) for 24 hr at 28° with *Rhizopus nigricans* (ATCC no. 6227b) in a medium containing peptone and corn molasses, furnished in ca. 70 per cent yield 11α-hydroxy-19-norprogesterone (II) (m.p. 171–173°, $[\alpha]_D$ + 62° ($CHCl_3$),‡ $\lambda_{max.}^{EtOH}$ 242 mμ, log ε 4·22; *Anal.* Found for

* Paper XC. H. J. Ringold, E. Batres and J. A. Zderic *Tetrahedron.* **2**, 164 (1958).

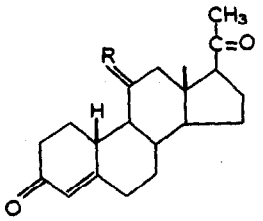
† New York Academy of Sciences Conference on *New Steroid Compounds with Progestational Activity*, New York City, October 7–8, 1957.

‡ The 11α-hydroxy assignment is also consistent with molecular rotation data: ΔM_D 11α-hydroxy-19-norprogesterone→19-norprogesterone +245 as compared to ΔM_D 11α-hydroxy-19-nortestosterone→19-nortestosterone +284.[6]

[1] C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer *J. Amer. Chem. Soc.* **76**, 4092 (1954); Abstracts, Milwaukee A.C.S. Meeting p. 18J, April, 1952; U.S. patents 2,744,122 and 2,774,777.
[2] F. B. Colton U.S. patent 2,725,389.
[3] A. J. Birch *Quart. Rev. Chem. Soc. Lond.* **4**, 69 (1950); *J. Chem. Soc.* 367 (1950).
[4] A. Zaffaroni, H. J. Ringold, G. Rosenkranz, F. Sondheimer, G. H. Thomas and C. Djerassi *J. Amer. Chem. Soc.* **76**, 6210 (1954).
[5] B. J. Magerlein and J. A. Hogg *J. Amer. Chem. Soc.* **79**, 1508 (1957).
[6] R. L. Pederson, J. A. Campbell, J. C. Babcock, S. H. Eppstein, H. C. Murray, A. Weintraub, R. C. Meeks, P. D. Meister, L. M. Reineke and D. H. Peterson *J. Amer. Chem. Soc.* **78**, 1512 (1956).
[7] C. Djerassi, L. Miramontes and G. Rosenkranz *J. Amer. Chem. Soc.* **75**, 4440 (1953).

$C_{20}H_{28}O_3$: C, 75·62; H, 8·87; O, 15·21) while similar treatment of (I) with *Curvularia lunata* (Syntex strain 192) provided 11β-hydroxy-19-norprogesterone (III) (m.p. 215–217°, $[\alpha]_D$ + 158° ($CHCl_3$), $\lambda_{max.}^{EtOH}$ 242 mμ, log ε 4·20; *Anal.* Found for $C_{20}H_{28}O_3$: C, 75·83; H, 8·81). Other strains of *Rhizopus nigricans* (ATCC no. 10404) as well as other organisms such as *Rhizopus arrhizus* (ATCC no. 11145), *Helicostylum piriforme* (ATCC no. 8992) and *Absidia coerulea* (ATCC no. 1359b) effected monohydroxylation of 19-norprogesterone.

The structure assignments follow from the following observations. Both (II) and (III) upon chromium trioxide oxidation furnished the same ketone, 11-keto-19-norprogesterone (IV) (m.p. 175–176°, $[\alpha]_D$ + 284° ($CHCl_3$), $\lambda_{max.}^{EtOH}$ 240 mμ, log ε 4·20, $\lambda_{max.}^{CHCl_3}$ 5·87, 6·0 and 6·16 μ; *Anal.* Found for $C_{20}H_{26}O_3$: C, 76·32; H, 8·31; O, 15·32), thus demonstrating that both hydroxylation products are epimers and that oxygenation did not occur at a tertiary carbon atom. The infrared spectrum of the common oxidation product (IV) requires that the newly introduced hydroxyl group forms part of a six-membered ring and the position of the ultraviolet absorption maxima of (II), (III) and (IV), which remain unchanged in alkali, as well as the stability of (II) and (III) towards alkali eliminate all positions except for C-11 and C-12. Since microbiological oxidation of a steroid at C-12 has so far not been observed,[8] the presence of an oxygen atom at C-11 in (II), (III) and (IV) appears to be established.

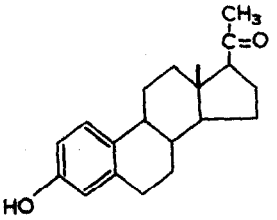


I R=H_2

II R=$\overset{OH}{H}$

III R=$\overset{OH}{H}$

IV R=O



V

The introduction of a double bond at positions 1 and 2 in Δ^4-3-keto steroids by microbiological means[9] is now well known. When applied to a 19-nor-Δ^4-3-keto steroid, such a reaction should lead directly to the corresponding phenol. In fact, such a transformation—in the case of 19-nortestosterone leading to estradiol and estrone—has been recorded very recently[9] and this enzymatic reaction may well be of biochemical significance in the formation of estrogens.

We have observed that such a microbiological aromatization proceeds with equal facility with 19-norprogesterone (I)[7] and that incubation of (I) for 72 hr with *Corynebacterium simplex* (ATCC no. 6946) produces in over 60 per cent yield by direct crystallization 3-hydroxy-17β-acetyl-1,3,5(10)-estratriene (V) (m.p. 238–240°, $[\alpha]_D$ + 164° ($CHCl_3$), λ_{max}^{EtOH} 280–282 mμ, log ε 3·30) identified by direct comparison with an authentic specimen.[10]

The preparation of hitherto inaccessible aromatic 11-oxygenated pregnenes by a combination of microbiological hydroxylation and dehydrogenation of 19-norpregnenes will be reported at a future date.

Research Laboratories
Syntex, S.A.
Apartado Postal 2679
Mexico, D.F.

A. Bowers
C. Casas-Campillo
Carl Djerassi

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[10] C. Djerassi, G. Rosenkranz, J. Iriarte, J. Berlin and J. Romo *J. Amer. Chem. Soc.* **73**, 1523 (1951).